REMARKS

Reconsideration of the present application in view of the above amendments and the following remarks is respectfully requested. Claims 18-22, 24-39 and 65 are currently pending and under consideration. By the present amendment, claims 33-36 are canceled. Claims 18, 37 and 39 are amended to more specifically recite certain aspects of the claimed invention, and claim 65 is amended to properly recite dependency, in light of the cancellation of claims 33-36. Support for these amendments is provided throughout the specification and claims as originally filed, and these amendments do not constitute new matter. Specific support for the antibodies recited in claim 1 is provided, *e.g.,* on page 3, line 26, to page 4, line 2. Support for the fusion protein being expressed as a soluble protein in the periplasmic space is provided, *e.g.,* on page 2, line 29, to page 3, line 1. These amendments are made without prejudice to filing a continuation, continuation-in-part, or divisional thereon.

Claim Objection

Claim 39 stands objected to for improper Markush language. Applicants thank the Examiner for noting this error. Accordingly, the claim has been amended to recite the term "and" instead of "or" as requested by the Examiner.

Rejection under 35 U.S.C.§ 112, Second Paragraph, Indefiniteness

Claims 33-37 and 65 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite, because claim 33 depends from claim 23, which has been canceled, and claims 34-37 and 65 depend from claim 33. Applicants thank the Examiner for noting this inconsistent dependency. Applicants note that claims 33-36 have been canceled without prejudice, and claim 37 has been amended to depend from claim 18 instead of claim 33. In addition, claim 65 has been amended to remove dependency from canceled claims 33-36. Applicants submit that these amendments render this basis of rejection moot and, thus, respectfully request reconsideration of these claims in view of the amendments.

Rejection under 35 U.S.C. §102(e), Anticipation

Claims 18-22, 24, 26, 28, 38, 39, and 65 stand rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,451,995 B1. More specifically, the Action alleges that U.S. Patent No. 6,451,995 B1 teaches a fusion protein comprising streptavidin and a single-chain antibody separated by a linker of at least 2 or 4 amino acids, which is capable of forming tetrameric complexes.

As an initial matter, Applicants reserve the right to submit, at a later date, evidence demonstrating that Applicants had possession of the claimed invention prior to the Section 102(e) date afforded U.S. Patent No. 6,451,995 B1. At present Applicants are gathering the appropriate information.

At this time, Applicants respectfully traverse this ground for rejection and submit that U.S. Patent No. 6,451,995 B1 fails to teach each element of the presently claimed invention and, therefore, fails to anticipate the instant claims. Applicants submit that the present invention is based upon their surprising discovery that recombinant streptavidin fusion proteins comprising genomic streptavidin, as opposed to "core" or truncated streptavidin sequences, are expressed as soluble proteins in the periplasmic space and, therefore, provide unexpected advantages in the expression and purification of such recombinant fusion proteins. However, U.S. Patent No. 6,451,995 B1 fails to teach streptavidin fusion proteins having the features that the streptavidin moiety includes at least 129 amino acids of streptavidin and are expressed as soluble proteins in the periplasmic space, as presently claimed.

It is respectfully submitted that U.S. Patent No. 6,451,995 B1 neither describes an appropriate streptavidin molecule, nor does it demonstrate that the streptavidin constructs described therein were soluble. In fact, a careful reading of the end of Example 1 and the beginning of Example 2 would clearly lead the skilled artisan to understand that the streptavidin fusion protein was not in the periplasm, since the authors utilized supernatant, periplasmic extract, and cell extract, in order to determine positive clones. If they had, in fact, identified that a large quantity of the streptavidin fusion protein had entered the periplasm, this would certainly not have gone unnoticed. Indeed, this aspect would have been emphasized given the difficulty of obtaining such soluble forms in the periplasm. Accordingly, viewing this patent in the best

possible light, it is unclear what it teaches about streptavidin conjugates, but it is clear that it does not teach how to make such conjugates soluble or the soluble fusion proteins presently claimed. In fact, there is no teaching in that regard whatsoever. Thus, Applicants respectfully submit that this patent fails to teach each and every aspect of the presently claimed invention.

Nevertheless, and solely in order to expedite allowance, Applicants have amended the claims to recite specific antigens to which the antibody portion of the claimed fusion protein is directed. Applicants submit that U.S. Patent No. 6,451,995 B1 clearly does not recite these specific antibodies, or fragments thereof, and, accordingly, fails to teach each element of the presently claimed invention, as required to establish anticipation under Section 102(e). Thus, Applicants respectfully request that this ground of rejection be withdrawn.

Rejection under 35 U.S.C. §103(a), Obviousness

Claims 18-21, 24, 26, 28, 29, 30, and 65 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Dubel *et al.* (J. Immunol. Meth. 178:201-209, 1995), as evidenced by Kipriyanov *et al.* (Human Antibod. Hybrid. 6:93-101, 1995), in view of Gallizia *et al.* (Protein Express. Purif. 14:192-196, 1998). Specifically, the Action alleges that Dubel *et al.* teaches a fusion protein comprising a portion of genomic streptavidin and an antibody or antigen-binding fragment thereof. Applicants note that the Examiner acknowledges that Dubel *et al.* does not expressly teach that the first polypeptide of the fusion protein comprises at least 129 amino acids of streptavidin, as set forth in SEQ ID NO: 2. Rather, the Examiner contends that Gallizia *et al.* teaches a fusion protein comprising residues 15 to 159 of streptavidin and a T7-tag peptide, which is expressed in *E. coli* as a soluble protein.

Applicants respectfully traverse this basis of rejection and submit that the presently claimed invention is not obvious in light of the cited references, either alone or in combination. Specifically, Applicants submit that the Action fails to establish a *prima facie* case of obviousness, since it fails to demonstrate that any of the reference teach or suggest their combination to produce the claimed fusion protein. As established by the courts and enunciated in the M.P.E.P., "[o]bviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention when there is some teaching, suggestion, or

motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art." M.P.E.P., 8th Ed. § 2143.01. In the present case, neither reference teaches, suggests or would motivate the skilled artisan to combine the references to achieve the claimed invention. The teaching or suggestion to make a claimed combination must be found in the prior art and not based upon the Applicant's disclosure. *In re Vaeck*, 947 F.2d 488 (Fed Cir. 1991). Since none of the references provide such requisite teaching, this basis of rejection appears to rest upon impermissible hindsight based upon the instant application's description of genomic streptavidin fusion proteins.

Further to this point, Applicants submit that Gallizia *et al.* merely provides some teaching that the introduction of a T7-tag peptide to core streptavidin results in increased solubility and ease of purification of the resulting proteins. Nowhere does Gallizia *et al.* provide any suggestion or recognition that streptavidin fusion proteins comprising at least 129 amino acids of streptavidin are more soluble than those comprising core streptavidin. Rather, it appears that the conclusion drawn by Gallizia *et al.* is that it is the presence of the T7-tag peptide that confers increased solubility. Thus, this combination of references provides no basis or motivation for the skilled artisan to modify the teachings of Dubel *et al.* related to a core streptavidin-antibody fusion protein by increasing the amount of streptavidin present in the fusion proteins, in order to achieve a more soluble fusion protein. Furthermore, Applicants also submit that Kipriyanov *et al.* clearly fails to remedy this deficiency. If anything, the cited combination of references could only motivate the skilled artisan to add a T7-tag peptide, as described by Gallizia *et al.*, to the fusion protein of Dubel *et al.* Applicants contend that this is not analogous to the claimed fusion proteins comprising antibodies or antibody fragments linked to genomic streptavidin and is, therefore, not a proper basis for this rejection. In view of this, Applicants request that the Examiner reconsider and withdraw this basis of rejection.

Claims 22, 25, 27, 31, and 32 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Dubel *et al.* (J. Immunol. Meth. 178:201-209, 1995), as evidenced by Kipriyanov *et al.* (Human Antibod. Hybrid. 6:93-101, 1995), in view of Gallizia *et al.* (Protein Express. Purif. 14:192-196, 1998), and further in view of Goshorn *et al.* (Cancer Res. 53:2123-2127, 1993), Ohno, *et al.* (DNA Cell Biol. 15:401-406, 1996), McLaughlin, *et al.* (Oncology

12:1763-1769, 1998), the Internet edition of the Bioprobe BV Catalog of Mouse Hybridomas (Bandung, Indonesia), and Desplancq *et al.* (Protein Eng. 7:1027-1033, 1994). The Action cites Dubel *et al.* and Gallizia *et al.* for the teachings described above, while alleging that the further references teach specific linkers and other limitations recited in the claims.

Applicants respectfully traverse this basis of rejection and submit that the Action has failed to establish a *prima facie* case of obviousness. For the reasons described above, Applicants submit that Dubel *et al.* and Gallizia *et al.* clearly provide no motivation to combine the references to achieve the claimed invention. Applicants further submit that the references cited in these further rejections also fail to provide any motivation to modify the fusion protein taught by Dubel *et al.* by using a longer streptavidin fragment. Again, it appears that the Examiner has engaged in impermissible hindsight reconstruction of the claimed invention. In pertinent part, it should again be emphasized that none of the cited references has identified the advantages of using genomic streptavidin in the context of recombinant antibody constructs. The reason is straightforward and simple; this is because the state of the art at the time this application was filed indicated that antibody-streptavidin fusions were substantially produced in bacteria as inclusion bodies that needed harsh denaturing and refolding techniques. If it were merely as easy as the Action posits to achieve soluble antibody-streptavidin fusions, then everyone producing such fusions would be doing so using genomic streptavidin. To argue to the contrary contravenes logic. No pharmaceutical company would produce a product by way of inclusion bodies that necessitate harsh denaturing and renaturing steps if they could simply use an alternative construct to produce the molecule in a soluble form in the periplasm. Accordingly, Applicants submit that the use of the various references to arrive at the claimed invention can only amount to hindsight reconstruction. If it were otherwise, all those performing streptavidin antibody fusions would have produced them with genomic streptavidin...which is simply not the case. In this regard, Applicants respectfully request that the Examiner withdraw this ground for rejection and pass the present claims to allowance.

Claims 18-22, 24, 26, 28-32, 38, 39, and 65 stand rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,451,995 B1, in view of Desplancq *et al.* (Protein Eng. 7:1027-1033, 1994).

Applicants respectfully traverse this basis of rejection and submit that the Action has failed to establish a *prima facie* case of obviousness. It is again respectfully submitted that U.S. Patent No. 6,451,995 B1 neither teaches nor describes an appropriate streptavidin molecule, nor does it teach or describe that the streptavidin constructs were soluble. In fact, a careful reading of the end of Example 1 and the start of Example 2 leads one to believe that the streptavidin-antibody molecule was not in the periplasm, as they utilized supernatant, periplasmic extract, and cell extract to determine positive clones. If they had, in fact, identified that a large quantity of the streptavidin antibody construct had entered the periplasm, this would not have gone unnoticed. Indeed, this aspect would have been emphasized given the difficulty of obtaining such forms soluble in the periplasm. Accordingly, viewing this patent in the best possible light, it is unclear what it teaches about streptavidin conjugates, but it is clear that it does not teach how to make such conjugates soluble. In fact there is no teaching in that regard whatsoever. Thus, Applicants respectfully submit that this patent fails to teach any aspect of the presently claimed invention. Nevertheless, and solely in order to expedite allowance, Applicants have amended the claims to recite specific antigens to which the antibody is directed. In light of these amendments, Applicants respectfully request that this ground of rejection be reconsidered and withdrawn.

Double Patenting Rejection

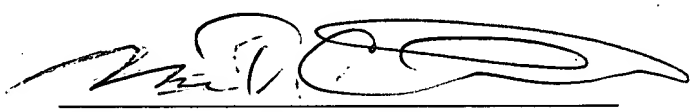
Applicants respectfully request that the provisional double-patenting rejections be held in abeyance until allowable subject matter is identified.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicants respectfully submit that all of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. If there is any further matter requiring attention prior to allowance of the subject application, the Examiner is respectfully requested to contact the undersigned attorney (at 206-622-4900) to resolve the matter.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC



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Enclosure:
Change of Status to Small Entity

Customer No. 00500

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